

## King's Research Portal

DOI:

[10.1176/appi.ajp.2018.17091006](https://doi.org/10.1176/appi.ajp.2018.17091006)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Crawford, M. J., Sanatinia, R., Barrett, B., Cunningham, G., Oliver, D., Ganguli, P., Lawrence-Smith, G., Leeson, V., Lemonsky, F., Lykomitrou, G., Montgomery, A., Morriss, R., Munjiza, J., Paton, C., Skorodzien, I., Singh, V., Tan, W., Tyrer, P., & Reilly, J. G. (2018). The clinical effectiveness and cost effectiveness of lamotrigine for people with borderline personality disorder: a randomized, placebo-controlled trial. *The American Journal of Psychiatry*, 175(8), 756-764. <https://doi.org/10.1176/appi.ajp.2018.17091006>

### Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### Take down policy

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

Total word count = 3476

Total tables and figures = 7

**The clinical effectiveness and cost effectiveness of lamotrigine for people with borderline personality disorder: A randomized, placebo-controlled trial.**

Mike J Crawford M.D. <sup>1\*</sup>, Rahil Sanatinia Ph.D.<sup>1</sup>, Barbara Barrett Ph.D.<sup>2</sup>, Gillian Cunningham B.Sc.<sup>3</sup>, Oliver Dale M.B. B.S. <sup>4</sup>, Poushali Ganguli M.Sc. <sup>2</sup>, Geoff Lawrence-Smith M.B. B.S. <sup>5</sup>, Verity Leeson Ph.D. <sup>1</sup>, Fenella Lemonsky<sup>1</sup>, Georgia Lykomitrou M.Sc.<sup>6</sup>, Alan A Montgomery Ph.D.<sup>7</sup>, Richard Morriss M.D. <sup>6</sup>, Jasna Munjiza Ph.D. <sup>1,8</sup>, Carol Paton B.Sc. <sup>5</sup>, Iwona Skorodzien M.Sc. <sup>6</sup>, Vineet Singh M.B B.S.<sup>9</sup>, Wei Tan M.Sc. <sup>7</sup>, Peter Tyrer M.D.<sup>1</sup>, Joseph G Reilly D.M.<sup>3</sup> on behalf of the LABILE study team.

1 Centre for Psychiatry, Imperial College London, Hammersmith Campus, London, W12 0NN, UK.

2 Centre for the Economics of Mental and Physical Health, King's College London, London, SE5 8AF, UK.

3 Tees, Esk & Wear Valley NHS Trust, Middlesbrough, TS6 0SZ, UK.

4 West London NHS Mental Health Trust, Southall, UB1 3EU, UK.

5 Oxleas NHS Foundation Trust, Dartford, DA2 7WG, UK.

6 Division of Psychiatry and Applied Psychology, University of Nottingham, Nottingham, NG7 2RD UK.

7 Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, NG7 2UH, UK.

8 Central and North West London NHS Foundation Trust, London NW1 2PL, UK.

9 Derbyshire Healthcare NHS Foundation Trust, Derby, DE22 3LZ, UK.

**Presentation at meetings:**

- 1) North American Society for the Study of Personality Disorder, New York. April 7-9<sup>th</sup> 2017.
- 2) British and Irish Group for the Study of Personality Disorder, Aberdeen. March 21<sup>st</sup>-23<sup>rd</sup> 2017.

**Correspondence and requests for reprints**

Professor Mike Crawford [m.crawford@imperial.ac.uk](mailto:m.crawford@imperial.ac.uk)

Centre for Psychiatry. Imperial College London (Hammersmith Campus)

Commonwealth Building, Du Cane Road, London W12 0NN United Kingdom

**Conflict of interest**

All authors have completed the Unified Competing Interest form (available on request from the corresponding author). All authors declare no other competing interests except Professor Joseph Reilly. Professor Reilly has received project funding from the Drug Safety Research Unit as part of an unrestricted grant provided by Merck Pharmaceuticals.

**Funding**

This study was supported by the National Institute of Health Research Technology Assessment Programme (12/167/95). The Imperial Biomedical Research Centre Facility which is funded by the National Institute of Health Research also provided support that have contributed to the research results reported within this paper. Part of RM's salary during the project was paid by NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands (CLAHRC EM).

**Role of the sponsor and the funder**

The sponsor of the study played no part in the preparation of this paper. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, or the Department of Health. A more detailed account of the study methods and findings will be published in full in Health Technology Assessment in 2018.

## **ABSTRACT (252 words)**

### ***Objectives***

To examine whether lamotrigine is a clinically effective and cost-effective treatment for people with borderline personality disorder.

### ***Method***

Multicentre, double-blind, placebo-controlled randomized trial. Between July 2013 to November 2016, we recruited 276 people aged 18 or over, who met diagnostic criteria for borderline personality disorder. We excluded those with co-existing bipolar affective disorder or psychosis, those already taking a mood stabiliser, and women at risk of pregnancy. We randomly allocated participants on a 1:1 ratio to up to 400mg of lamotrigine per day or an inert placebo using a remote web-based randomization service. The primary outcome was total score on the Zanarini Rating scale for Borderline Personality Disorder (ZAN-BPD) at 52 weeks. Secondary outcomes included depressive symptoms, deliberate self-harm, social functioning, health-related quality of life, resource use and costs, side effects of treatment and adverse events.

### ***Results***

195 (70.6%) participants were followed up at 52 weeks, at which point 49 (36%) of those prescribed lamotrigine and 58 (42%) of those prescribed placebo were taking it. Mean total ZAN-BPD score was 11.3 (SD = 6.6) among those randomized to lamotrigine and 11.5 (SD = 7.7) among those randomized to placebo (adjusted difference in means = 0.1, 95% C.I = -1.8 to 2.0,  $p=0.91$ ). There was no evidence of any differences in secondary outcomes. Costs of direct care for those prescribed lamotrigine were similar to those prescribed placebo.

### ***Conclusions***

Treating people with borderline personality disorder with lamotrigine is not a clinically effective or cost-effective use of resources.

### ***Trial registration***

Current Controlled Trials ISRCTN78923965.

## Introduction

Borderline personality disorder is a severe mental disorder that is characterised by sudden distressing changes in mood, unstable relationships and impulsivity (1, 2). Levels of substance misuse and deliberate self-harm and suicide are high among people with borderline personality disorder. The condition occurs globally, with a lifetime community prevalence of over 5% (3). While no drugs have been formally approved for the treatment of borderline personality disorder, people with this condition are prescribed large amounts of medication (4), with as many as 90% being prescribed psychiatric drugs and two-thirds taking long-term antipsychotic drugs (5-7).

Rapid changes in mood are one of the hallmarks of borderline personality disorder (8). This has led to interest in the possibility that mood stabilisers, which improve the mental health of people with bipolar disorder, could also help those with borderline personality disorder (9). Current practice guidelines on the treatment of borderline personality disorder advocate use of mood stabilisers for the treatment of impulsive aggression and self-harming behaviors (10, 11). A systematic review of pharmacotherapy for people with borderline personality disorder concluded that mood stabilisers may be effective in reducing core symptoms of the condition (12). but trials to date have been small and have not examined long term effects (9).

Lamotrigine is an anticonvulsant that is licensed for the treatment of bipolar affective disorder. It is relatively safe in overdose and less teratogenic than some other mood stabilisers (13-15). Evidence that lamotrigine may prevent relapse in rapid-cycling bipolar disorder (16), makes it particularly worthy of testing among people with borderline personality disorder. Two small randomized trials reported reduced impulsivity and affective lability compared to an inactive placebo (17, 18). However both were preliminary studies which only examined short-term effects.

We investigated the clinical and cost-effectiveness of lamotrigine for adults with borderline personality disorder who were using secondary care mental health services. We followed people up 52 weeks after randomization to examine the long-term effects of this treatment.

## **Methods**

The LABILE (Lamotrigine And Borderline personality disorder: Investigating Long-term Effects) trial was a two-arm, parallel group, blinded, randomized trial of lamotrigine versus placebo for adults with borderline personality disorder. Full details of the trial protocol have been published elsewhere (19). We recruited people aged 18 or over who were in contact with mental health services in the United Kingdom. To take part in the study potential participants had to meet DSM-IV diagnostic criteria for borderline personality disorder using the Structured Clinical Interview for Axis II Personality Disorders (20). Potential participants were excluded if they met diagnostic criteria for bipolar affective disorder (type I & II) assessed using the Structured Clinical Interview for Axis I Disorders, or psychotic disorder (21), were prescribed a mood stabiliser currently or within the last four weeks, had a known history of liver or kidney impairment, or had cognitive or language difficulties that prevented them from providing informed consent. We also excluded any pre-menopausal women who were breastfeeding or pregnant at the time of the baseline assessment, contemplating becoming pregnant during the following 12 months, or sexually active and unwilling to take regular contraception. Approval for the research was given by the London Central Research Ethics Committee (Ref: 12/LO/1514) and from the Research and Development departments of the participating provider organizations. The Medicines and Healthcare Products Regulatory Agency (MHRA) gave Clinical Trial Authorisation.

### ***Randomization and blinding***

After consenting to participate, eligible patients were asked to complete the Hypomanic Checklist (22), a short screening questionnaire that can distinguish those with bipolar disorder from those

with unipolar depression, and the International Personality Disorder Examination (IPDE) screening questionnaire (23), Local research staff accessed an automated randomization service operated by Nottingham Clinical Trials Unit that randomly allocated participants in a 1:1 ratio to either lamotrigine or placebo. This employed random permuted blocks of varying size, stratified by study centre, severity of personality disorder (using data from the IPDE and criteria developed by Tyrer and Johnson) (24), and extent of bipolarity (using a score of more or less than 14 on the Hypomania Checklist) (22).

The randomization system generated a unique code for each participant corresponding to a predetermined active or placebo allocation. Site pharmacies were unblinded to allocation and would cross-reference the predetermined list held in pharmacy with each trial prescription detailing the participant's randomization code, allowing selection of trial medication from the appropriate arm. Bottles were blinded at the point of dispensing by removal of a tear-off label which contained a code that identified the contents as lamotrigine or placebo in a coded format.

All patients, carers and referring psychiatrists were blinded to treatment assignment until 52 weeks post randomization except in instances where there was an overdose, pregnancy or other adverse event that required disclosure. Researchers collecting follow-up data remained blind in these circumstances. Blinding of researchers, trial manager and trial statistician was maintained until all data entry and processing were completed and the database had been locked. All study researchers, aside from the trial statistician and health economist, remained blind to allocation status until after an initial discussion of trial findings had been completed.

### ***Intervention***

All those taking part in the study continued to receive usual treatment which included contact with primary and secondary health services including access to psychological treatment services and



inpatient admission if required. No restrictions were imposed on the use of other treatments, except that they were not prescribed lamotrigine (aside from trial medication) or any other antiepileptic mood stabiliser. In addition, those randomized to the active arm of the trial were prescribed up to 200 mg of generic lamotrigine titrated over a six week period depending on how well it was tolerated and clinical response. Treatment dose was titrated according to the established British National Formulary protocol (25) but standardised to 14-day intervals. The starting dose was 25mg per day. Depending on response and tolerance this was increased to 50mg after two weeks, 100mg after four weeks and 200mg thereafter. In keeping with recommendations, the maintenance dose for women taking the combined oral contraceptive pill was increased to 400mg daily (25). Those randomized to control treatment received usual treatment plus a prescription for an inert placebo, which was identical in appearance but contained lactose monohydrate.

In the light of evidence linking adverse skin reactions with patients abruptly starting high doses of lamotrigine, we required participants who had a break in treatment of more than five days to re-titrate medication from 25mg daily.

### ***Outcomes***

The primary outcome was symptoms of borderline personality disorder measured at twelve months using total score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (26). The ZAN-BPD is a widely used measure of symptoms and behavioural problems experienced by people with this condition. The total range of scores is 0 to 36 with higher scores indicating poorer mental health. The ZAN-BPD has been used in previous studies of pharmacological and psychological treatments for people with borderline personality disorder and is sensitive to change (27). The lead researcher (RS) was trained to use the ZAN-BPD and supervised all other researchers on the project. We examined the degree of agreement between scores on the ZAN-BPD from the pairs of researchers who separately rated 27 participants and found these to be highly correlated (Intraclass Correlation Coefficient = 0.98, 95% CI = 0.95 to 0.99).

The secondary outcomes were total score on the ZAN-BPD at three, six and twelve months after randomization, together with depression, measured using the Beck Depression Inventory (28), deliberate self-harm using the Acts of Deliberate Self-Harm Inventory (29), social functioning using the Social Functioning Questionnaire (30), use of alcohol and other drugs using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (31) and health-related quality of life using the EQ-5D-3L (32). Researchers assessed side effects of trial medication when interviewing participants using a proforma designed to cover the possible effects listed in the British National Formulary entry for lamotrigine (25). Higher scores on all secondary outcomes indicate poorer health or functioning, aside from the EQ-5D-3L for which higher scores indicate lower health-related quality of life. Adverse events were also recorded. Use of health and social care resources and costs were assessed using a modified version of the Adult Service Use Schedule (33). This questionnaire is used to collect detailed data on use of all hospital and community services including medication. All secondary outcomes were assessed three, six, and twelve months after randomization except alcohol and drug use which was assessed at baseline and twelve months later.

### ***Adherence***

Researchers maintained regular contact with participants throughout the follow-up period enquiring about side effects and adherence every fortnight, during the initial titration phase, and then monthly once a maintenance dose had been reached. Participants were asked if they had missed doses of medication and a log was made of the dose dispensed on each occasion. We used these logs to record the number of weeks participants reported taking trial medication and the dose of medication they reported taking each week. We defined adherence with medication as the participant taking uninterrupted medication at a dose of 100mg or more throughout the study period after the initial titration phase had been completed. We supplemented these data by asking study participants to complete the Morisky Medication 4-item Adherence Scale at three, six and twelve months (34). This is a four item questionnaire which provides a valid estimate of

adherence with psychotropic medication (35). Total score ranges from 0 to 4 with higher scores indicating higher adherence.

### ***Statistical analysis***

The sample size calculation and all data analyses were conducted using Stata versions 13 and 14 (36). In a previous trial of problem solving therapy improvements in mental health and reduced use of emergency medical services were seen among those who had a 3.6 point reduction in total ZAN-BPD score. We needed primary outcome data from 214 participants at 52 weeks to have 90% power to detect a minimal clinically relevant difference of 3.0 (SD = 6.75) in total score on the ZAN-BPD using a 0.05 two-sided level of statistical significance. To take account of 15% loss to follow-up we increased the target sample size to 252.

Details of the statistical analyses were recorded in the Statistical Analysis Plan which was agreed by with the independent Trial Steering Committee prior to completion of data collection, database lock and unblinding of the study.

The primary analysis was performed according to randomized treatment, regardless of adherence with allocation and without imputation of missing data. The analysis was adjusted by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and the extent of bipolarity (score  $\geq 14$  or  $< 14$ ). For secondary analysis of ZAN-BPD scores groups were compared using a mixed model for repeated outcome measures adjusted by the same stratification variables used for the primary analysis. We investigated whether any treatment effects were sustained or emerged later by including an interaction term between treatment with lamotrigine and time in the model. In the absence of a time effect, the effectiveness parameter was the average difference in mean ZAN-BPD score over the 52 week period along with 95% confidence interval and p value. Further sensitivity analyses were conducted to adjust for any variable with marked imbalance at baseline and investigate the impact of missing data, using multiple imputation.

We investigated the effect of treatment adherence using complier average causal effect (CACE) estimation methods according to whether the participant had taken trial medication at a dose of 100mg or more without interruption during the 52 weeks prior to the final follow-up interview. The primary cost-effectiveness analysis involved comparing incremental differences in total costs and incremental differences in mental health assessed using the ZAN-BPD. In a secondary cost-utility analysis we compared incremental differences in costs with differences in quality of life measured using Quality Adjusted Life Years derived from the EQ-5D-3L.

Analyses of secondary outcomes used similar methods to those in the primary analysis. We used general linear models for continuous outcomes and logistic regression models for binary outcomes and regression models with bootstrapping for cost data.

For safety data including Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions we used summary statistics, i.e. number of adverse events/side effects of different categories, number and proportion of participants reported at least one Adverse Events or Serious Adverse Events within each treatment arm.

The trial is registered with Controlled Clinical Trials as ISRCTN90916365.

## **Results**

Between July 2013 and October 2015, 296 patients were screened for eligibility. Of these, 276 (93.2%) met eligibility criteria and were randomized (figure 1); 137 to lamotrigine plus usual care and 139 to placebo plus usual care. There were no instances in which researchers were unblinded to the participants' allocation status prior to completion of collection of 52 week outcome data.

Baseline demographic and clinical characteristics of study groups were comparable (table 1). Follow up rates were similar between treatment arms with 195 (71%) participants completing the 52 week

follow up (fig. 1). In total 93 (33.7%) participants took trial medication as per protocol and similar proportions were seen in both arms (table 2). At 12 weeks, 68.8% were taking trial medication regularly, with 38.9% taking it regularly at 12 months.

There was a decrease in ZAN-BPD at 12 weeks, after which it remained stable throughout the remainder of the follow up. Total scores on ZAN-BPD in the lamotrigine arm of the trial were 11.5 at 12 weeks, 11.9 at 24 weeks and 11.3 at 52 weeks. Corresponding scores among those in the control arm of the trial were 11.5, 11.9 and 11.5 (see figure 2). No difference was found in total ZAN-BPD score at 52 weeks between treatment arms. No difference was found in any of the secondary outcomes, nor in the four sub scores of the ZAN-BPD at any time point (table 3 and supplementary tables S1-S4). The lack of treatment effect was supported by sensitivity analyses. Adjusted difference in mean ZAN-BPD was 0.0 (95% CI = -1.25 to 1.26,  $p = 0.90$ ) using repeated measures, -0.1 (95% CI = -1.9 to 1.8) using multiple imputation for missing data and 0.3 (95% CI = -3.7 to 4.3) when adjusted for adherence. Regarding adverse events, 77 (56%) of those in the lamotrigine arm of the trial had one or more event, compared to 93 (67%) of those in the control arm of the trial (table 4). The corresponding figures for serious adverse events were 26 (19%) in the active arm of the trial and 32 (23%) in the control arm, including five pregnancies (three in the lamotrigine group and two in the control group).

At baseline, costs were on average \$8,160 in the lamotrigine group and \$5,163 in the placebo group in the six months prior to randomization. Average total costs over 52 weeks were \$17,785 in the lamotrigine group and \$12,340 in the control arm of the trial (table 5). The difference in cost was not statistically significant (adjusted difference = \$931.99, 95% CI = -2,740.44 to 4,604.41,  $p=0.62$ ). Group differences between health-related quality of life and the resulting Quality Adjusted Life Years were also not statistically significant.

## **Discussion**

In this placebo-controlled randomized trial, we found no evidence that prescribing lamotrigine to people with borderline personality disorder led to improvements in their mental health. The study was large enough to generate a precise estimate of the overall treatment effect, which did not include the minimum clinically important difference of 3.0 on the ZAN-BPD at 12 months (the primary outcome measure). Levels of adherence to trial medication were low with only a third (n = 93, 33.7%) of study participants taking trial medication throughout as specified in the study protocol. Levels of adherence were higher during the first 12 weeks of the study when two-thirds of participants were taking the medication (n = 190, 68.8%), but we did not find differences in study outcomes during this period. In a secondary analysis using Complier Average Causal Effect methods we found no evidence that greater adherence to trial medication was associated with any benefit to patients. Most participants reported one or more adverse effects, but those in the lamotrigine arm of the trial were no more likely to report potential side effects than those in the placebo arm of the trial.

### ***Strengths and limitations of the study***

The LABILE trial is the first ever phase III trial of a mood stabiliser for people with borderline personality disorder. One of the main strengths of the study is that we followed participants up over a 12 month period. Borderline personality disorder is a long-term condition but previous drug trials have not examined long-term outcomes (12). We recruited 11% more participants than we originally planned and the study size allowed precision to exclude a minimum clinically significant difference in the severity of symptoms of borderline personality disorder.

In this pragmatic trial we attempted to replicate clinical practice. However one area where we were unable to do this was in the means by which participants obtained their medication. Rather than collecting medication from a local pharmacy most participants had medication delivered to them in person or by post. This meant that participants had more regular contact with staff than they would have done in normal clinical practice. While levels of adherence to medication were low in this trial we believe that the additional contact that participants had with researchers meant that they may have been higher than would be seen in routine clinical practice.

### ***Comparison with results of previous trials***

In contrast to the results of the LABILE study, the two previous randomized trials of lamotrigine for people with borderline personality disorder both reported positive effects (17, 18). Both trials were smaller, had a larger number of exclusion criteria and followed participants up for a shorter period of time. Several factors may explain differences in the results of the LABILE study and the two previous studies. Randomization does not guarantee that treatment arms are balanced in small trials and it is possible that differences in study outcomes in these previous trials resulted from differences in baseline characteristics of the samples. Secondly, in this pragmatic trial we deliberately kept our exclusion criteria to a minimum. This approach meant that we were able to recruit people with the type of complex and severe problems that people with borderline personality disorder who use speciality mental health services generally have. It is possible that lamotrigine reduces symptoms of borderline personality disorder among people who have less complex and severe mental health problems than we recruited to the study. In the LABILE trial we had a rigorous process for maintaining blinding through the use of an automated web-based system that allocated study participants. Methods used to maintain blinding in previous trials are unclear (17).

### ***Implications for clinicians***

At present most people with borderline personality disorder who are in contact with mental health services are being prescribed psychiatric drugs (7); with a quarter being prescribed unlicensed mood stabilisers (5). Use of lamotrigine is specifically recommended in some textbooks on the treatment of people with borderline personality disorder (11). Clinicians may feel under considerable pressure to prescribe medication for people with borderline personality disorder especially at times of crisis (6). In the absence of clear evidence suggesting benefits associated with any type of medication, non-pharmacological approaches should be offered (2, 9).

Reductions in symptoms of borderline personality disorder during the course of the trial are in keeping with the results of longitudinal studies showing that the mental health of people with this condition improves over time (37, 38). However the pattern of improvement among study participants, with reductions in symptoms during the first 12 weeks of the trial, suggests that regression to the mean or general factors such as instillation of hope may have been responsible for this improvement.

In the LABILE trial we took great care not to recruit women who were pregnant, wanting to become pregnant or were pre-menopausal, sexually active and unwilling to take regular contraception. Despite the assurances that participants gave us, five subsequently became pregnant during the trial. While lamotrigine has been shown to be relatively safe in pregnancy, this is not true of all mood stabilisers – notably sodium valproate (39). Warnings have been issued about the use of off-licence sodium valproate to women of child bearing age (40). Despite this a recent national audit showed that over 10% of women with borderline personality disorder who are in contact with secondary care mental health services in the UK are currently being prescribed this drug (5). Data from the LABILE trial emphasises the importance of avoiding use of unlicensed medications that are potentially teratogenic for women with borderline personality disorder who are of child bearing age.



## ***Conclusions***

Based on the results of this trial we do not recommend that people with borderline personality disorder are prescribed lamotrigine. While pharmacological treatment of coexisting mental health conditions is important, we did not find evidence to support the use of lamotrigine for treatment the core symptoms of borderline personality disorder.

## **Contributors**

MJC, RS, BB, FL, VL, RM, CP, PT and JGR were involved in all parts of the study. WT, AAM, BB and PG were involved in data analysis and revising the manuscript. RS, GC, GL, JM and IS were involved in recruiting study participants and revising the manuscript. OD, GL-WS and VS were principle investigators and were also involved in revising the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. MJC is the guarantor.

We thank all those who took part in the study and clinical staff at Central and North West London NHS Foundation Trust, Derbyshire Healthcare NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, Oxleas NHS Foundation Trust, Tees Esk & Weir Valley NHS Foundation Trust and West London NHS Mental Health Trust for their help with completing the study, especially Ms Lauren Bryant, Ms Adele Mason, Mr John Lawton, Dr Ben Lucas, Dr Paul Mallett, Dr Tom McLaren, Dr Ayodeji Morah, Dr Bal Powar, Dr Paola Rossin, Dr Zahir Shah, and Ms Danielle Wilson.

We thank the Clinical Research Network for publicising the study and supporting the recruitment and follow-up of study participants. We would especially like to thank Pat Daly, Anthony Davis, Tara Harvey, Bianca Hinds-Walters, Natalie Marking, Antoinette McNulty, Lorraine O'Connell, Sandra Simpson, Lisa Thompson, and Audrey Williamson for supporting study recruitment, and helping with participant follow-up. We also thank members of the trial coordinating team at Imperial College London including Claudia Adele, Amy Claringbold, Zoe Cotton, Kavi Gakhal, Ana Arbeloa del Moral, Lesley O'Connell and Dilveer Sually for overseeing the administration of the trial.

We are grateful to all members of the Trial Steering Committee (Maxine Patel (Chair 2013-15), Paul Moran (Chair 2015-16), Delia Bishara, Oliver Dale, Sandra O'Sullivan, Jenny Trite) the Data Monitoring and Ethical Committees (Nicol Ferrier (Chair), Tony Johnson and Steve Pearce) for their support and guidance. We are grateful to Sally Strange and Jennie Parker for their input to the

project as experts by experience: to Sally for advising on study logistics and to both Sally and Jennie for helping us interpret and communicate study findings.

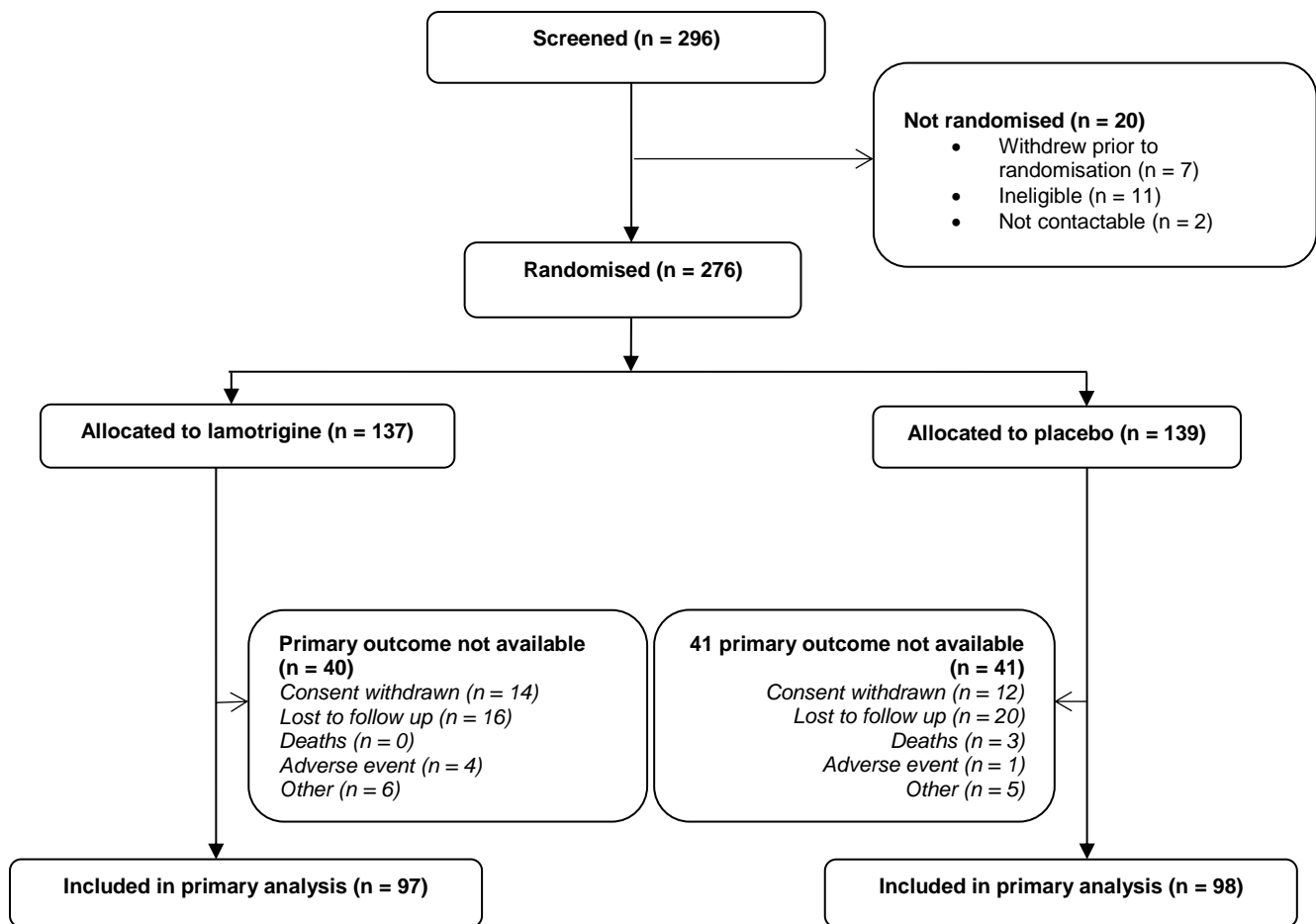
## REFERENCES

1. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet*. 2004;364:453-61.
2. Gask L, Evans M, Kessler D. Clinical Review. Personality disorder. *BMJ*. 2013;347:f5276.
3. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69(4):533-45.
4. Sansone RA, Rytwinski D, Gaither GA. Borderline personality and psychotropic medication prescription in an outpatient psychiatry clinic. *Compr Psychiatry*. 2003;44(6):454-8.
5. Paton C, Crawford MJ, Bhatti SF, Patel MX, Barnes TR. The use of psychotropic medication in patients with emotionally unstable personality disorder under the care of UK mental health services. *Journal of Clinical Psychiatry*. 2015;76:512-8.
6. Crawford MJ, Kakad S, Rendell C, Mansour NA, Crugel M, Liu KW, et al. Medication prescribed to people with personality disorder: the influence of patient factors and treatment setting. *Acta Psychiatrica Scandinavica*. 2011;124:396-402.
7. Bender DS, Dolan RT, Skodol AE, Sanislow CA, Dyck IR, McGlashan TH, et al. Treatment utilization by patients with personality disorders. *American Journal of Psychiatry*. 2001;158:295-302.
8. Zimmerman M, Multach M, Dalrymple K, Chelminski I. Clinically useful screen for borderline personality disorder in psychiatric out-patients. *The British Journal of Psychiatry* 2017;210:165-6.
9. Crawford MJ, MacLaren T, Reilly JG. Are mood stabilisers helpful in treatment of borderline personality disorder? *BMJ*. 2014;349:g5378 doi: 10.1136/bmj.g5378.
10. Association AP. Practice guideline for the treatment of patients with borderline personality disorder. *American Journal of Psychiatry*. 2001;158 (suppl.):1-52.
11. Gunderson JG, Links PS. *Borderline Personality Disorder: A Clinical Guide*. Washington, D.C.: American Psychiatric Pub, Inc.; 2008 2001.
12. Lieb K, Vollm B, Rucker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *Br J Psychiatry*. 2010;196(1):4-12.
13. Sukumaran S, Herbert J, Tracey J, Delanty N. Safety of newer generation anti-epileptic drugs in non-accidental overdose: an Irish population study. *Seizure*. 2005;14(3):151-6.
14. Tomson T, Battino D, French J, Harden C, Holmes L, Morrow J, et al. Antiepileptic drug exposure and major congenital malformations: the role of pregnancy registries. *Epilepsy Behav*. 2007;11(3):277-82.
15. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *NEngl J Med*. 2009;360(16):1597-605.
16. Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *The Journal of clinical psychiatry*. 2000;61(11):841-50.
17. Tritt K, Nickel C, Lahmann C, Leiberich PK, Rother WK, Loew TH, et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J Psychopharmacol*. 2005;19(3):287-91.
18. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int Clin Psychopharmacol*. 2009;24(5):270-5.
19. Crawford MJ, Sanatinia R, Barrett B, Byford S, Cunningham G, Gakhal K, et al. Lamotrigine versus inert placebo in the treatment of borderline personality disorder: study protocol for a randomized controlled trial and economic evaluation. *Trials*. 2015;16:308.
20. First MB, Spitzer RL, Gibbon M, Williams JBW, Benjamin L. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*, version 2.0. New York 1994.

21. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version. New York Biometrics Research.: New York State Psychiatric Institute; 2002.
22. Gamma A, Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, et al. Transcultural validity of the Hypomania Checklist-32 (HCL-32) in patients with major depressive episodes. *Bipolar Disord*. 2013;15(6):701-12.
23. Loranger A. International Personality Disorder Examination (IPDE) Manual. White Plains, NY: Cornell Medical Center, 1995.
24. Tyrer P, Johnson T. Establishing the severity of personality disorder. *AmJPsychiatry*. 1996;153(12):1593-7.
25. BNF. British National Formulary 74. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2017.
26. Zanarini MC, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. *Journal of Personality Disorders*. 2003;17:233-42.
27. Blum N, St John D, Pfohl B, Stuart S, McCormick B, Allen J, et al. Systems Training for Emotional Predictability and Problem Solving (STEPPS) for outpatients with borderline personality disorder: a randomized controlled trial and 1-year follow-up. *Am J Psychiatry*. 2008;165(4):468-78.
28. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years later. *Clinical Psychology Review*. 1988;8:77-100.
29. Davidson KM. Cognitive Therapy for Personality Disorders: A Guide for Clinicians. Second Edition. Hove: Routledge; 2007.
30. Tyrer P, Nur U, Crawford M, Karlsen S, McLean C, Rao B, et al. The Social Functioning Questionnaire: a rapid and robust measure of perceived functioning. *International Journal of Social Psychiatry*. 2005;51:265-75.
31. Newcombe DAL, Humeniuk RE, Ali R. Validation of the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): report of results from the Australian site. *Drug and alcohol review*. 2005;24:217-26.
32. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37:53-72.
33. Borschmann R, Barrett B, Hellier JM, Byford S, Henderson C, Rose D, et al. Joint crisis plans for people with borderline personality disorder: feasibility and outcomes in a randomised controlled trial. *The British Journal of Psychiatry* 2013;202:357-64.
34. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.
35. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *BrJ Clin Pharmacol*. 2000;50(2):166-71.
36. StataCorp. Stata, Version 13. College Station, TX: StataCorp, 2013.
37. Gunderson JG, Stout RL, McGlashan TH, Shea MT, Morey LC, Grilo CM, et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. *Arch Gen Psychiatry*. 2011;68(8):827-37.
38. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Time to attainment of recovery from borderline personality disorder and stability of recovery: A 10-year prospective follow-up study. *Am J Psychiatry*. 2010;167(6):663-7.
39. Harden CL. Antiepileptic drug teratogenesis: what are the risks for congenital malformations and adverse cognitive outcomes? *Int Rev Neurobiol*. 2008;83:205-13.
40. Medicines and Healthcare products Regulatory Agency. Medicines related to valproate: risk of abnormal pregnancy outcomes. Drug Safety Update. 2015;8:1.



Figure 1 CONSORT diagram



**Table 1: Summary characteristics of study participants by intervention group**

Characteristic	Lamotrigine		Placebo	
	N/ mean	%/ SD	N/ mean	%/ SD
<b>Mean age in years at randomization (SD)</b>	36.0	11	36.2	11
<b>Gender:</b> Male	34	25	34	24
Female	103	75	105	76
<b>Ethnicity:</b> White	123	90	123	90
Black	7	5	4	3
Asian	1	1	2	1
Other	6	4	10	7
<b>Employment status*:</b> Employed	34	25	26	19
Unemployed	95	69	105	76
Student	4	3	1	1
Retired	2	1	2	1
<b>Severity of personality disorder:</b> Simple	0	0	2	1
Complex	137	100	137	99
<b>ZAN-BPD* (mean, SD)</b>	16.6	5.8	17.4	6.2
<b>Beck Depression Inventory* (mean, SD)</b>	39.8	11.7	38.4	10.2
<b>Deliberate self-harm in previous six months</b>	96	70	51	37
<b>Current alcohol misuse: yes</b>	53	39	54	39
<b>Current drug misuse: yes</b>	54	39	47	34
<b>Social functioning score* (mean)</b>	15.0	4.1	14.9	4.5

ZAN-BPD - Zanarini rating scale for Borderline Personality Disorder

SD = Standard deviation

\*Missing data: n = 137 lamotrigine and 134 placebo

# Missing data: n = 72 lamotrigine and 75 placebo



**Table 2: Adherence to trial medication**

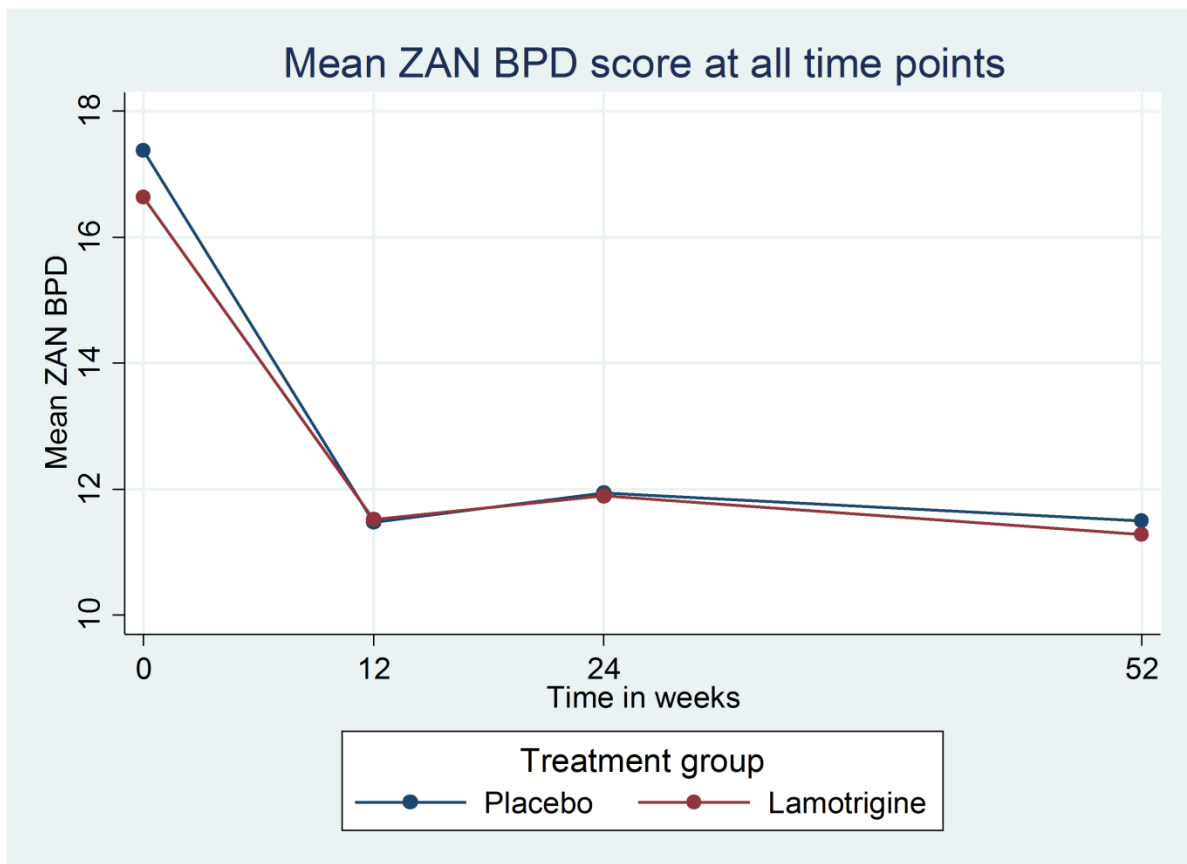
	Lamotrigine		Placebo	
	N/ mean	%/ IQR	N/ mean	%/IQR
<b>Study medication received per protocol*</b>	44	32	49	35
<b>Morisky Rating scale at 12 month<sup>#</sup></b> Median [IQR]	3	2,4	3	2,4
<b>Number of weeks participants received study medication</b> Median [IQR]	32	9, 52	46	7,52
<b>Number receiving medication throughout first 12 weeks</b>	95	69	95	68
<b>Number receiving medication 40 to 52 weeks</b>	49	36	58	42
<b>Dose of medication at 12 weeks in mg</b> Median [IQR]	200	200, 200	200	200, 200
<b>Dose of medication at 52 weeks in mg</b> Median [IQR]	200	200,200	200	200,200

IQR = Inter quartile range

\*Following initial titration participant stayed on a dose of 100mg or more throughout the remainder of the study

<sup>#</sup> Missing data: n = 88 lamotrigine and 82 placebo

Figure 2. Change in total ZAN-BPD score at 12, 26 and 52 weeks.



**Table 3: Primary and secondary outcomes at 52 weeks**

	Lamotrigine		Placebo		*Adjusted difference	95% Confidence Intervals	p-value
	N/ mean	%/ SD	N/ mean	%/ SD			
Zanarini Scale for Borderline Personality Disorder	11.3	6.6	11.5	7.7	0.1	-1.8, 2.0	0.906
Beck Depression Inventory [SD]	28.8	16.1	28.7	15.5	-0.2	-4.5,4.1	0.937
Deliberate self-harm in last 6m (n, %)	45	46	8	39	1.25	0.68, 2.28	0.464
Social Functioning Questionnaire	12.4	4.3	12.3	4.9	0	-1.2, 1.2	0.987
Alcohol use <sup>#</sup>	28	31	22	25	1.4	0.7, 2.7	0.354
Any other drug use <sup>#</sup>	27	30	23	26	1.2	0.6, 2.3	0.598
Quality Adjusted Life Years	0.467	0.300	0.511	0.269	-0.012	-0.057, 0.034	0.612

\*Adjusted by site and other stratification factors. Estimate is difference in means for continuous outcomes, and odds ratio for binary outcomes. Severity was not included in the model for self-harm, alcohol use and any other substance use due to collinearity.

Summary statistics is mean [SD] for continuous outcomes and N (%) for binary outcomes.

\*Missing data: n = 83 lamotrigine and 77 placebo

**Table 4: Summary of adverse events among study participants by intervention group** by Medical Dictionary for Regulatory Activities (MedDRA) classifications

	Lamotrigine	Placebo
<b>Total number of adverse events</b>	246	285
<b>Total number of participants with at least one adverse event</b>	77	93
<b>Total number of adverse events by system organ class</b>		
Blood and lymphatic system disorders	2	3
Cardiac disorders	0	1
Endocrine disorders	0	1
Eye disorders	1	6
Gastrointestinal disorders	38	55
General disorders and administration site conditions	14	14
Hepatobiliary disorders	1	0
Immune system disorders	1	1
Infections and infestations	23	38
Injury, poisoning and procedural complications	17	39
Investigations	7	3
Metabolism and nutrition disorders	2	1
Musculoskeletal and connective tissue disorders	8	7
Nervous system disorders	32	31
Pregnancy, puerperium and perinatal conditions	3	2
Psychiatric disorders	37	40
Renal and urinary disorders	1	0
Reproductive system and breast disorders	3	1
Respiratory, thoracic and mediastinal disorders	16	9
Skin and subcutaneous tissue disorders	35	31
Social circumstances	1	1
Surgical and medical procedures	4	1

**Table 5. Total costs (USD) per participant over the 52-week follow-up period**

<b>Component of care</b>	<b>Lamotrigine (n=83) Mean</b>	<b>Standard deviation</b>	<b>Placebo (n=77) Mean</b>	<b>Standard deviation</b>	<b>*Difference</b>	<b>*95% Confidence Interval</b>
Lamotrigine	352.49	139.42	0	0	355.54	323.48, 387.58
Inpatient hospital care	10594.45	3086.82	6842.90	14608.42	605.33	-2612.27, 3822.92
Community care	5858.45	5228.02	5056.83	4489.41	230.86	-636.05, 1097.76
Other medication	979.11	3568.90	439.58	1410.41	34.47	-439.94, 508.87
Total	17784.51	25335.14	12339.33	16484.23	931.92	-2740.24, 4604.08

\*Adjusted for by site, baseline ZAN-BPD score, severity of personality disorder and score on the HCL (score $\geq$ 14 or <14)